

Prognostic Value of Dobutamine–Atropine Stress Echocardiography Early After Acute Myocardial Infarction

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Objectives. The aim of this multicenter, multinational, prospective, observational study was to assess the relative value of myocardial viability and induced ischemia early after uncomplicated myocardial infarction.

Background. Dobutamine–atropine stress echocardiography allows evaluation of rest function (at baseline), myocardial viability (at low dose) and residual ischemia (peak dose, up to 40 μ g with atropine up to 1 mg) in one test.

Methods. Dobutamine–atropine stress echocardiography was performed 12 ± 5 days (mean \pm SD) after a first uncomplicated acute myocardial infarction in 778 patients (677 men; mean age 58 ± 10 years) with technically satisfactory rest echocardiographic study results. Patients were followed-up for 9 ± 7 months.

Results. Dobutamine–atropine stress echocardiographic findings were positive for myocardial ischemia in 436 of patients (56%) and negative in 342 (44%). During follow-up, there were 14 cardiac-related deaths (1.8% of the total cohort), 24 (2.9%) nonfatal myocardial infarctions and 63 (8%) hospital readmissions for unstable angina. One hundred seventy-four patients (22%) underwent coronary revascularization (bypass surgery or coronary angioplasty). Spontaneous events occurred in 61 of 436 patients with positive and 40 of 342 patients with negative findings

on dobutamine–atropine stress echocardiography (14% vs. 12%, $p = 0.3$). When only spontaneously occurring events were considered, the most important predictor was myocardial viability (chi-square 9.7). Using the Cox proportional hazards model, only the presence of myocardial viability (hazard ratio [HR] 2.0, $p < 0.002$) and age (HR 1.03, $p < 0.001$) were predictive of spontaneously occurring events. When only hard cardiac events were considered, age was the strongest predictor (chi-square 3.6, $p = 0.056$), followed by wall motion score index (WMSI) at peak dose (chi-square 3.3, $p = 0.06$) and remote ischemia (chi-square 2.25, $p = 0.1$). When cardiac death was considered, WMSI at peak dose was the best predictor (HR 9.2, $p < 0.0001$).

Conclusions. During dobutamine stress, echocardiographic recognition of myocardial viability is more prognostically important than echocardiographic recognition of myocardial ischemia for predicting unstable angina, whereas WMSI at peak stress was the best predictor of cardiac-related death. Different events can be recognized with different efficiency by various stress echocardiographic variables.

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In patients with myocardial infarction, left ventricular function at rest (1,2), myocardial viability (3–6) and inducible wall motion abnormalities (7) have recognized prognostic significance. Pharmacologic stress echocardiography with titrated dobutamine infusion provides the unique opportunity of an integrated assessment of these three variables: Rest function can be evaluated at baseline; myocardial viability can be

identified at the low dose stage as a functional improvement in regions with rest dyssynergy (8); and myocardial ischemia can be recognized at high doses as wall motion dysfunction (9). Noninvasive risk stratification of patients recovering from an uncomplicated myocardial infarction remains a major challenge for clinical cardiologists (10). To date, data on the prognostic value of dobutamine stress echocardiography in this subset of patients are limited (11,12) and have several limitations, thus blunting their impact on clinical practice: small sample size; the need to include subjective end points, such as revascularization procedures, to document prognostic power; the highly selected nature of the patients studied to date and the inclusion of patients with clinical complications in whom any form of stress testing may be redundant (10).

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Abbreviations and Acronyms

CI	= confidence interval
ECG	= electrocardiogram, electrocardiographic
HR	= hazard ratio
WMSI	= wall motion score index

In the present study, the capability of dobutamine-atropine stress echocardiography for prognostic stratification early after an acute myocardial infarction was evaluated in a large-scale multicenter, multinational, observational study design on the basis of evidence collected by 14 different echocardiographic laboratories, all with established experience in stress echocardiography and meeting the quality control requirements for stress echocardiographic interpretation (7). A total of 778 patients were evaluated 12 ± 5 days (mean \pm SD) after a first acute myocardial infarction and were followed up for 9 ± 7 months.

Methods

Patients. The initial cohort included 1,362 patients admitted to the coronary care unit for episode of acute myocardial infarction. Of these 1,362, 159 were excluded for continuing myocardial ischemia, left ventricular failure, shock or important cardiac arrhythmias. Of the remaining 1,203 patients, 34 had a technically poor acoustic window at baseline, making dobutamine-atropine stress echocardiography unfeasible; 224 were excluded for age >75 years; 58 did not undergo stress testing because of refusal to take the test or for logistic reasons; 71 experienced a reinfarction. An additional 38 patients were eligible for dobutamine-atropine stress echocardiography but were subsequently lost to follow-up. Therefore, from January 1, 1992 to October 1, 1994, we studied 778 consecutive patients (101 women, 677 men, mean $[\pm$ SD] age 58 ± 10 years) with a clinically uncomplicated first acute myocardial infarction, baseline echocardiographic findings of satisfactory quality and available follow-up information. The primary rest and stress findings in the study patients are reported in Table 1. All patients underwent dobutamine-atropine stress echocardiography after 12 ± 5 days from a first uncomplicated acute myocardial infarction (no continuing myocardial ischemia, left ventricular failure, shock or important cardiac arrhythmias). It is known that these features identify a high risk subset on the basis of clinical characteristics alone and that specialized noninvasive testing has the greatest potential independent value for risk stratification in patients without these clinical features (10). According to individual needs and physician choices, 648 patients were evaluated after discontinuation of antianginal drugs, and 130 were evaluated during antianginal treatment (nitrates or calcium antagonists or beta-adrenergic blocking agents, alone or in combination).

Dobutamine-atropine stress echocardiography. After a rest electrocardiogram (ECG) and echocardiogram were ac-

Table 1. Rest and Dobutamine Stress Findings in 778 Study Patients

Age (yr)	58 ± 10
Range	30–87
Male/female	677/101
Q wave MI	572 (73%)
Non-Q wave MI	206 (26%)
Thrombolytic therapy	450 (58%)
WMSI at rest	1.5 ± 0.3
Positive DASE findings	436 (56%)
WMSI at viability assessment	1.4 ± 0.3
WMSI at peak dobutamine	1.7 ± 0.4
ECG changes during DASE	499 (70%)
Chest pain during DASE	107 (14%)

Data presented are mean value \pm SD or number (%) of patients. DASE = dobutamine-atropine stress echocardiography; ECG = electrocardiographic; MI = myocardial infarction; WMSI = wall motion score index.

quired, intravenous access was secured, and dobutamine was infused with 3-min dose increments, starting from $5 \mu\text{g/kg}$ body weight per min and increasing to 10, 20, 30, $40 \mu\text{g/kg}$ under continuous ECG and echocardiographic monitoring. When no end point was reached, atropine (in four divided doses of 0.25 mg up to a maximum of 1 mg) was added to the continuing $40\text{-}\mu\text{g/kg}$ dobutamine infusion. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography with a 16-segment model (13). In all studies, segmental wall motion was semiquantitatively graded as follows: normal = 1; hypokinetic, marked reduction of endocardial motion and thickening = 2; akinetic, virtual absence of inward motion and thickening = 3; and dyskinetic, paradoxical wall motion away from the center of the left ventricle in systole = 4. The wall motion score index (WMSI) was derived by dividing the sum of individual segment scores by the number of interpretable segments (13). *Test positivity* was defined as the occurrence of at least one of the following conditions: 1) new dyssynergy in a region with normal rest function (i.e., normokinesia becoming hypokinesia, akinesia or dyskinesia); 2) worsening of rest dyssynergy (i.e., hypokinesia becoming akinesia or dyskinesia; rest akinesia becoming dyskinesia was not considered a positivity criterion) (14); 3) biphasic response of a rest dyssynergy (i.e., hypokinesia showing normal function at low dose with a following deterioration at high dose; or akinesia becoming hypokinesia at low dose and returning to the initial condition at high dose) (15). Test positivity was defined as “remote” ischemia when the development of asynergy was not directly adjacent to the infarct area and was assumed to be related to another vascular region (16). Nonechocardiographic diagnostic end points were the following (17): peak atropine dose; 85% of target heart rate; achievement of conventional (severe chest pain or diagnostic ST segment changes, or both). The test was also stopped, in the absence of diagnostic end points, for one of the following reasons of submaximal, nondiagnostic test results (17): 1) intolerable symptoms; and 2) limiting asymptomatic side effects, including a) hypertension (systolic blood pressure >220 mm Hg; diastolic blood pressure >120 mm Hg); b)

hypotension (relative or absolute: >30-mm Hg decrease in blood pressure); c) supraventricular arrhythmias (supraventricular tachycardia or atrial fibrillation); d) ventricular arrhythmias (ventricular tachycardia; frequent, polymorphous premature ventricular beats).

The presence of *myocardial viability* was defined as an improvement in regional function of 1 grade or more at low dose dobutamine (up to 10 $\mu\text{g/kg}$ per min; i.e., a hypokinetic segment becoming normal or an akinetic segment becoming hypokinetic).

Echocardiographic monitoring was performed throughout dobutamine infusion and up to at least 5 min after the end of the infusion. Two-dimensional echocardiographic images were recorded at baseline and at the end of each dobutamine step. For each patient, left ventricular function was evaluated at baseline, at low dose for the assessment of myocardial viability in dyssynergic segments and at peak stress.

Quality control of stress echocardiographic readings.

Quality control of the diagnostic performance at the different centers was of critical importance to acquire meaningful information for the data bank. In the enrolled centers, quality control was performed according to two criteria, both of which had to be met to fulfill the quality control requirements (7,17).

The first criterion was tested on a videotape with 20 stress echocardiographic studies prepared at the coordinating center (Institute of Clinical Physiology, Pisa). For all 20 studies the interpretation of two experienced independent observers (E.P., A.P.) was concordant as to presence and site of dyssynergy, and the stress results were in full agreement with the presence and site of coronary stenoses during coronary angiography. The unanimous reading of the two observers was arbitrarily assumed to be the reference standard against which the interpretations from each participating center were evaluated. The observers from each center interpreted the videotape in a blinded manner, with no access to either clinical and angiographic data or the interpretation of other observers. It was assumed a priori that the minimal threshold of concordance to satisfy this part of the quality control had to be $\geq 90\%$.

The second criterion consisted of a random sampling of 20 consecutive studies from each contributing center. These 20 studies were examined in blinded manner by an experienced cardiologist-echocardiographer at each coordinating center whose reading was arbitrarily assumed to be the reference standard. It was assumed a priori that the minimal threshold of concordance to satisfy the quality control criteria had to be $\geq 80\%$. The lower concordance cutoff is due to the fact that this second set of tapes was not selected on the basis of the superior quality but was randomly sampled from each center in a consecutive manner. All the 14 enrolled centers met the minimal requirements of quality control.

Follow-up data. Follow-up data were obtained from at least one of four sources: review of the patient's hospital record; personal communication with the patient's physician and review of the patient's chart; telephone interview with the patient conducted by trained personnel; or patient visits to staff physicians at regular intervals in the outpatient clinic (7).

Events were defined as cardiac-related death, nonfatal myocardial infarction and unstable angina. For patients who died in the hospital or at home, the cause of death was elucidated from the medical record, the family and the local physician who signed the death certificate. The definition of *cardiac-related death* required documentation of significant arrhythmias or cardiac arrest, or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. In case of death out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. *Myocardial infarction* was defined as a cardiac event requiring admission to the hospital, with development of new ECG changes and cardiac enzyme level increases. *Unstable angina* was defined by accelerating anginal symptoms requiring hospital readmission (no enzyme level elevation or new wall motion dyssynergy on the resting echocardiogram or new Q waves on the rest ECG) or progression of symptoms requiring revascularization. Therefore, the *outcome events* were hard cardiac events (defined as cardiac-related death or nonfatal myocardial infarction) for infarction-free survival and spontaneously occurring events (death, nonfatal myocardial infarction, unstable angina) for spontaneous event-free survival. Only the most severe outcome was considered an end point when follow-up was censored at revascularization procedures.

There is controversy over whether coronary artery bypass surgery and coronary angioplasty should be considered cardiac events. They are likely to reflect the presence of severe disease. However, the decision to perform these procedures may be subjective and not by itself an adverse outcome. Therefore, the data were analyzed after exclusion of revascularization procedures.

Statistical analysis. Results are expressed as mean value \pm SD. The individual effects of certain variables on event-free survival were evaluated with the use of the Cox regression model (BMDP 2L, Department of Biomathematics, University of California at Los Angeles, revised 1987). The analysis was performed according to the unmodified forward-selection stepwise procedure. In this case, the variables were entered in to the model on the basis of a computed significance probability; accordingly, the variable that has the most significant relation to dependent outcome is selected first for inclusion in the model, and a solution to the functional form of the equation is computed. At the second and subsequent steps, the set of variables remaining at each point is evaluated, and the most significant is included if it improves the prediction of the outcome (*dependent variable*), but in this case this probability is conditional on the presence of the variable already selected. The algorithm ceases to select variables when there is no further significant improvement in the prediction of the whole model.

Variables selected for examination were age, gender, history of angina, thrombolysis, Q wave myocardial infarction, WMSI at rest, WMSI at viability, presence of myocardial viability, dobutamine-atropine stress echocardiographic positivity, WMSI at peak dobutamine, dobutamine time (i.e., test

duration to time of echocardiographically detected ischemia), remote ischemia.

Continuous variables were compared by the unpaired two-sample *t* test. Proportions were compared by the chi-square statistic; a Fisher exact test was used when appropriate. Kaplan-Meier life-table estimates of spontaneously occurring event-free survival was used to summarize the follow-up experience in these patients and to clarify presentation. Differences in survival curves were tested with the Mantel-Haenszel statistic. A *p* value <0.05 was considered statistically significant.

Results

The main rest and stress echocardiographic data are reported in Table 1.

Feasibility and tolerability of dobutamine-atropine stress echocardiography. In 43 patients, the test was submaximal for occurrence of limiting side effects; the test results of these patients (6% of all studies) were included in the analysis. Four patients had a major adverse reaction (ventricular fibrillation in one, acute myocardial infarction in one, ventricular tachycardia in two, as described in detail previously (17).

Rest echocardiographic findings. The rest WMSI was 1.47 ± 0.3 . Patients with Q wave infarction (*n* = 572, Table 1) tended to have a higher WMSI than those with non-Q wave infarction (*n* = 206): 1.53 ± 0.3 versus 1.30 ± 0.3 , *p* = NS.

Low dose findings. At the low dose stage (10 μ g/kg per min of dobutamine), the WMSI was 1.4 ± 0.3 (*p* < 0.01 vs. rest WMSI). Two-hundred sixty-four patients showed echocardiographic evidence of myocardial viability, of whom 205 had a Q wave infarction with a mean WMSI of 1.62 ± 0.3 , and 59 had a non-Q wave infarction with a mean WMSI of 1.45 ± 0.3 (*p* = NS).

High dose findings. Four-hundred thirty-six patients had positive findings on dobutamine-atropine stress echocardiography, of whom 379 had new (i.e., a normokinetic region becoming hypokinetic, akinetic, or dyskinetic) or worsening (i.e., hypokinetic region becoming akinetic or dyskinetic) dys-synergy, and 57 had a “biphasic” response (i.e., an akinetic region at rest improving at low dose and again becoming akinetic at peak stress).

Among the 342 patients with positive findings on dobutamine-atropine stress echocardiography, 46 had a positive finding before or at 9 min (corresponding to a dobutamine dose ≤ 20 μ g/kg per min), and 390 had a positive finding after 9 min (corresponding to a dobutamine dose of 30 to 40 μ g/kg per min, including atropine coadministration with the latter dose). Three-hundred forty patients had homozonal positivity, and 96 showed remote ischemia. The average WMSI at peak dobutamine-atropine stress echocardiography was 1.7 ± 0.4 .

Follow-up data. Patients were followed up for 9 ± 7 months (range 1 to 59 months). During the follow-up period, 14 patients died of cardiac-related causes; 24 had a nonfatal myocardial infarction; 63 developed unstable angina; and 174 underwent a coronary revascularization procedure (bypass

Table 2. Event Rate Occurrence in Relation to Dobutamine-Atropine Stress Echocardiographic Results

	DASE		<i>p</i> Value
	Positive Findings (<i>n</i> = 436)	Negative Findings (<i>n</i> = 342)	
Cardiac-related death	10 (2.2%)	4 (1.2%)	0.2
Nonfatal MI	11 (2.5%)	13 (4%)	0.3
Unstable angina	40 (9%)	23 (7%)	0.3
Revascularization procedures (PTCA and CABG)	123 (28%)	51 (15%)	0.001

Data presented are number (%) of patients. CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

surgery or coronary angioplasty) (Table 2). Patients with remote ischemia experienced 17 spontaneous events (18%) (4 cardiac-related deaths, 5 nonfatal myocardial infarctions, 8 repeat hospital admissions for unstable angina), whereas patients with peri-infarct test positivity experienced 39 spontaneous events (14%) (6 cardiac-related deaths, 4 nonfatal myocardial infarctions, 29 repeat hospital admissions for unstable angina). Revascularization procedures were more frequently undertaken in patients with remote ischemia and in those with peri-infarct ischemia (36% vs. 26%, *p* < 0.04). Patients with a biphasic response (*n* = 57) experienced five spontaneous events (two myocardial infarctions, three repeat hospital admissions for unstable angina).

Cardiac-related death. When cardiac-related death was considered, there were 10 events in patients with positive test results versus 4 events in those with negative test results (2.2% vs 1.1%, *p* = 0.2). By univariate analysis, WMSI at peak dose reached the highest value (chi-square 15.1, *p* = 0.0001). By stepwise analysis, the most important predictor was again WMSI at peak dose (chi-square 15.1, hazard ratio [HR] 9.2, 95% confidence interval [CI] 2.85 to 29.7, *p* < 0.0001), followed by age (chi-square 6.9, HR 1.08, 95% CI 1.01 to 1.15, *p* < 0.009) (Table 3).

Hard cardiac events. When only hard cardiac events (cardiac death, nonfatal myocardial infarction), were considered, there were 10 cardiac-related deaths and 11 nonfatal myocardial infarctions in patients with positive test results versus 4 cardiac deaths and 13 nonfatal myocardial infarctions in those with negative test results (5% vs. 5%, *p* = 0.9). Patients with remote ischemia (9%) had a higher incidence of hard events than those with homozonal positivity (4%, *p* < 0.02 vs. remote ischemia) or negativity for myocardial ischemia (5%, *p* = 0.1 vs. remote and homozonal positivity). By univariate analysis,

Table 3. Stepwise Predictors of Cardiac Death

	Chi-Square	<i>p</i> Value	HR (95% CI)
Peak WMSI	15.1	0.0001	9.2 (2.85–29.7)
Age	6.9	0.009	1.08 (1.01–1.15)

CI = confidence interval; HR = hazard ratio; WMSI = wall motion score index.

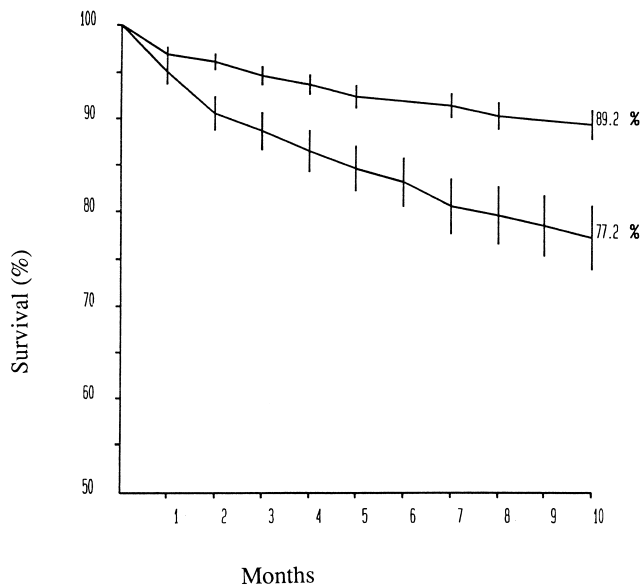


Figure 1. Cumulative survival rates free of spontaneously occurring events (including death, reinfarction and unstable angina) in patients with absence (**top curve**) and presence (**bottom curve**) of myocardial viability, recognized as functional improvement in a segment with rest wall motion abnormalities after low dose dobutamine. The presence of myocardial viability is associated with a greater incidence of events ($p < 0.05$).

age yielded the highest predictive value (chi-square 3.6, $p = 0.056$), followed by WMSI at peak dose (chi-square 3.35, $p = 0.06$) and remote ischemia (chi-square 2.25, $p = 0.1$). By stepwise analysis, the most important predictors were WMSI at peak stress (chi-square 3.186, HR 2.4, 95% CI 1.07 to 5.62, $p < 0.07$) and remote ischemia (chi-square 2.89, HR 0.5, 95% CI 0.27 to 1.11, $p < 0.08$) after age and male gender.

Spontaneous events. Patients with positive test results had a higher incidence of spontaneous events than those with negative results, but this difference did not reach statistical significance (14% vs. 12%, $p = 0.3$ [10 cardiac-related deaths, 11 nonfatal myocardial infarctions, 40 repeat hospital admissions for unstable angina in patients with positive results vs. 4 cardiac deaths, 13 nonfatal myocardial infarctions, 23 repeat hospital admissions for unstable angina in patients with negative results]). By univariate analysis, the most important predictors were the presence of myocardial viability (chi-square 9.71, $p < 0.0018$), followed by age (chi-square 8.76, $p < 0.0031$) and peak WMSI (chi-square 7.86, $p < 0.0051$). Other variables, such as lytic therapy versus no lytic therapy (chi-square 0.91, $p = 0.3$) or Q wave versus non-Q wave infarction (chi-square 0.01, $p = 0.9$), were not statistically significant.

By stepwise analysis, the most important predictor was again the presence of myocardial viability (chi-square 9.7, HR 2.0, 95% CI 1.39 to 3.12, $p < 0.002$), followed by age (chi-square 11.4, HR 1.03, 95% CI 1.01 to 1.05, $p < 0.001$). In Figure 1, the cumulative survival rates free of spontaneously occurring events in patients with and without myocardial viability are reported ($p < 0.05$ between the two groups).

Discussion

In patients evaluated early after a first acute uncomplicated myocardial infarction, the presence of myocardial viability detected by dobutamine stress echocardiography is associated with an increased incidence of unstable angina. The induction of remote ischemia is associated with an increased incidence of cardiac-related death and reinfarction—hard events that are not predicted by the presence of myocardial viability in this group of patients.

Prognostic meaning of inducible ischemia: comparison with previous studies. Peak dobutamine WMSI offers an integrated assessment of the extent and severity of left ventricular dysfunction at peak stress correlated to the extent and severity of the underlying coronary artery disease (16,18,19) and is the strongest predictor of subsequent cardiac-related death. This finding is in keeping with the large body of evidence from several studies demonstrating the usefulness of stress echocardiography in risk stratification early after acute myocardial infarction, using different stressors, such as exercise (20,21), transesophageal atrial pacing (22) and dipyridamole (7,23–26). In particular, the presence of extensive myocardial ischemia detected by dipyridamole stress echocardiography was associated with subsequent hard cardiac events in a large-scale multicenter, multinational, observational study in close to 1,000 patients (7,27), showing that peak WMSI was the strongest predictor of subsequent cardiac-related death. In the present study, we found that the stratification capability of dobutamine-induced ischemia was substantially better for cardiac-related death than for myocardial infarction or unstable angina. This finding further emphasizes the pathophysiologic heterogeneity of different cardiac events, which cannot all be predicted by a single variable. Stress testing assesses coronary stenoses by reflecting the physiologic consequences but cannot predict events largely unrelated to plaque size, such as thrombus, ulceration or fissuration, which can lead to abrupt coronary occlusions (28). The risk of reinfarction can be predicted weakly by inducible wall motion abnormalities (29), and the newly infarcted area matches the “area at risk” identified as ischemic during stress echocardiography only in a minority of cases (30). However, the fatal impact of occlusion will be very different according to the coronary atherosclerotic “milieu” detected by stress echocardiographic results.

Prognostic meaning of myocardial viability: comparison with previous studies. After the pioneering study of Pierard et al. (8), several groups have confirmed that wall motion response to dobutamine in a region with rest dysfunction is highly sensitive and specific for predicting the functional recovery of segmental contraction seen at late follow-up echocardiography (16). In light of this evidence, it would be expected that myocardial viability would carry a potential positive prognostic impact. If a segment has an inotropic reserve after dobutamine, it is likely to recover, and left ventricular function—a major prognostic determinant—will improve. In the present study, myocardial viability, identified as contractile recovery after low dose dobutamine, predicted the recurrence of angina,

although it was not associated with hard cardiac events. This finding is in keeping with previous studies (3–6), in which myocardial viability was identified by nuclear medicine techniques in patients with previous myocardial infarction. In those studies, myocardial viability showed an adverse prognostic value, even stronger than residual ischemia (4,6). It is conceivable that residual viable myocardium after myocardial infarction may act as an unstable substrate for further events unless it undergoes revascularization (6). In contrast, the beneficial prognostic effect of functional recovery is mild, if any, in patients with preserved global left ventricular function, present on the flat part of the hyperbolic curve relating left ventricular function to cardiac death (2). Our patients had a mean rest WMSI of 1.5, indicating preserved left ventricular function. More recently Williams et al. (6) demonstrated that viable or ischemic myocardium detected on dobutamine echocardiography in patients with left ventricular dysfunction is associated with an adverse prognosis, consistent with the findings of the present study showing that echocardiographically assessed myocardial viability can “paradoxically” affect prognosis in a negative manner.

Clinical implications. Survivors of acute myocardial infarction constitute a large, readily identifiable subset of patients in whom prognosis ultimately depends on the extent of residual ischemia, left ventricular dysfunction and presence of myocardial viability. Patients with either overt heart failure or ongoing myocardial ischemia have an adverse outcome and should be managed with an aggressive diagnostic and therapeutic approach. In the vast majority of patients who are asymptomatic after acute myocardial infarction, an early functional evaluation with stressing procedures is mandatory. The viability information is especially useful in predicting recurrence of angina. The echocardiographic positivity for ischemia occurring in a territory different from the infarct-related artery and WMSI at peak stress are more frequently associated with hard events. Different prognostic end points can be recognized with variable efficiency by different stress echocardiographic variables, further emphasizing that the pathophysiologic mechanisms of cardiac-related death, reinfarction and angina are not likely to be the same (28). The echocardiographic recognition of myocardial viability is more important for predicting softer events, whereas recognition of myocardial ischemia is more important for predicting harder prognostic end points.

References

1. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331–6.
2. Volpi A, De Vita C, Franzosi MG, et al., the Ad Hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza Nell'infarto Miocardico (GISSI)-2 data base. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis: results of the GISSI-2 data base. *Circulation* 1994;88:416–29.
3. Eitzman D, Al-Aouar Z, Kanter HL, et al. Clinical outcome of patients with advanced coronary artery disease. *J Am Coll Cardiol* 1992;20:559–65.
4. Tamaki N, Kawamoto M, Takahashi N, et al. Prognostic value of an increase in fluorine-18 deoxyglucose uptake in patients with myocardial infarction: comparison with stress thallium imaging. *J Am Coll Cardiol* 1993;22:1621–7.
5. Di Carli MF, Davidson M, Little R, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. *Am J Cardiol* 1994;73:527–33.
6. Williams MJ, Marwick T, Odabashian J, Lauer MS, Thomas J. Prognostic value of dobutamine echocardiography in patients with left ventricular dysfunction. *J Am Coll Cardiol* 1996;27:132–9.
7. Picano E, Landi P, Bolognese L, et al., on Behalf of the EPIC Study Group. Prognostic value of dipyridamole-echocardiography early after uncomplicated myocardial infarction: a large scale multicenter trial. *Am J Med* 1993;11:608–18.
8. Pierard LA, De Landsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol* 1990;15:1021–31.
9. Mannering D, Cripps T, Leech G, et al. The dobutamine stress test as an alternative to exercise testing after acute myocardial infarction. *Br Heart J* 1988;59:521–6.
10. De Busk RF. Specialized testing after recent acute myocardial infarction. *Ann Intern Med* 1989;110:470–81.
11. Sonel AF, Sawada S, Kovacs R, et al. Assessment of post-infarction prognosis using dobutamine stress echocardiography [abstract]. *Circulation* 1994;90 Suppl I:I-453.
12. Carlos ME, Smart SC, Stoiber TC, Toy A, Sagar KB. Dobutamine stress echocardiography for risk stratification following acute myocardial infarction [abstract]. *J Am Coll Cardiol* 1994;23 Suppl:297A.
13. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. (American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-dimensional Echocardiograms.) *J Am Soc Echocardiogr* 1989;2:358–67.
14. Arnesen M, Fioretti PM, Cornel JH, Postma-Tjoa J, Reijns AEM, Roelandt JRTC. Akinesis becoming dyskinesis during high-dose dobutamine stress echocardiography: a marker of myocardial ischemia or a mechanical phenomenon? *Am J Cardiol* 1994;73:896–9.
15. Senior R, Lahiri A. Enhanced detection of myocardial ischemia by stress dobutamine echocardiography utilizing the “biphasic” response of wall thickening during low and high dose dobutamine infusion. *J Am Coll Cardiol* 1995;26:26–32.
16. Picano E. *Stress Echocardiography*. 2nd ed. Heidelberg: Springer-Verlag, 1996.
17. Picano E, Mathias W, Pingitore A, Bigi R, Previtali M, on Behalf of the EDIC (Echo Dobutamine International Cooperative) Study. Safety and tolerability of dobutamine-atropine stress echocardiography: a prospective, multicenter study. *Lancet* 1994;344:1190–2.
18. Marwick TH, d'Hondt A, Baudhuin T, Willemart B, Wijns W, Detry JM. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography, scintigraphy or both? *J Am Coll Cardiol* 1993;22:159–67.
19. Panza JA, Curiel RV, Laurienzo JM, Quyyumi AA. Relation between ischemia threshold measured during dobutamine stress echocardiography and known indices of poor prognosis in patients with coronary artery disease. *Circulation* 1995;92:2095–103.
20. Jaarsma W, Visser CA, Funke Kupper AJ, Res JCI, Van Eenige MJ, Roos JP. Usefulness of two-dimensional exercise echocardiography shortly after myocardial infarction. *Am J Cardiol* 1986;57:86–90.
21. Ryan T, Armstrong WF, O'Donnell JA, Feigenbaum H. Risk stratification after acute myocardial infarction by means of exercise two-dimensional echocardiography. *Am Heart J* 1987;114:1305–16.
22. Iliceto S, Caiati C, Ricci A. Prediction of cardiac events after uncomplicated myocardial infarction by cross sectional echocardiography during transesophageal pacing. *Int J Cardiol* 1990;28:33–45.
23. Bolognese L, Rossi L, Sarasso G, et al. Silent versus symptomatic dipyridamole-induced ischemia after myocardial infarction: clinical and prognostic significance. *J Am Coll Cardiol* 1992;19:953–9.
24. Chiarella F, Domenicucci S, Bellotti P, Bellone P, Scarsi G, Vecchio C. Dipyridamole echocardiographic test performed 3 days after an acute myocardial infarction: feasibility, tolerability, safety and in-hospital prognostic value. *Eur Heart J* 1994;15:842–50.
25. van Daele MERM, McNeill AJ, Fioretti PM, et al. Prognostic value of dipyridamole sestamibi single-photon emission computed tomography and

- dipyridamole stress echocardiography for new cardiac events after an uncomplicated myocardial infarction. *J Am Soc Echocardiogr* 1994;7:370-80.
26. Neskovic AN, Popovic AD, Babic R, Marinkovic J, Obradovic V. Positive high dose dipyridamole echocardiography test after acute myocardial infarction is an excellent predictor of cardiac events. *Am Heart J* 1995;129:31-9.
27. Camerieri A, Picano E, Landi P, et al. Prognostic value of dipyridamole echocardiography early after myocardial infarction in elderly patients. *J Am Coll Cardiol* 1993;22:1809-15.
28. Fuster V, Badimon J, Chesebro J. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326:242-50.
29. Picano E, Pingitore A, Sicari R, et al., on Behalf of the Echo Persantine International Cooperative (EPIC) Study Group. Stress echocardiography results predict risk of reinfarction early after uncomplicated acute myocardial infarction: large scale multicenter study. *J Am Coll Cardiol* 1995;26:908-13.
30. Varga A, Picano E, Cortigiani L, et al., on Behalf of the EPIC (Echo Persantine International Cooperative) and EDIC (Echo Dobutamine International Cooperative) Study Groups. Is stress echocardiography capable to predict the site of future myocardial infarction? A large scale multicenter study. *J Am Coll Cardiol* 1996;28:45-51.